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Secondary Rituximab-associated vs. primary immunodeficiencies: the enigmatic border

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Abstract

Rituximab (RTX), a chimeric monoclonal antibody targeting CD20-positive cells, is a valuable treatment option for malignant and benign immune-related disorders. The rationale of targeting the CD20 antigen relies on depletion of both healthy and autoreactive/malignant CD20-espressing cells, but normal B cell reconstitution is expected within months after treatment. Nevertheless, a number of recent studies have documented prolonged B cell deficiency associated with new-onset hypogammaglobulinemia in patients receiving RTX. Awareness of post-RTX hypogammaglobulinemia has become wider among clinicians, with a growing number of reports about the increased incidence, especially in children. Although these patients were previously regarded as affected by secondary/iatrogenic immunodeficiency, atypical clinical and immunological manifestations (e.g. severe or opportunistic infections; prolonged B cell aplasia) raise concerns of delayed manifestations of genetic immunological disorders that have been unveiled by B cell perturbation. As more patients with undiagnosed primary immune deficiency (PID) receiving RTX have been identified, it remains the challenge in discerning those that might display a higher risk of persistent RTX-associated hypogammaglobulinemia and need a tailored immunology follow-up. In this review we summarize the principal evidence regarding post-RTX hypogammaglobulinemia and provide a guideline for identifying patients at higher risk of RTX-associated hypogammaglobulinemia that could harbor an inborn error of immunity.

RTX and emergent B cell-targeting biologicals

Over the last decades, a wide range of biologicals targeting B cells have gradually become available for the treatment of B cell lymphoproliferative diseases and autoimmune disorders [1]. The principal B-cell targeting agents with their current indications are summarized in **Table I**. Most described mechanisms of action include: (I) antibody-dependent cellular cytotoxicity (ADCC), (II) antibody-dependent cellular phagocytosis (ADCP), (III) complement direct cytotoxicity (CDC) (IV) transmembrane signaling and apoptosis induction (**Fig. 1).** Among B cell-targeting biologicals, Rituximab (RTX) represents the cornerstone for the treatment of CD20-positive malignancies and various autoimmune disorders. It is a chimeric monoclonal antibody which carries out its immunosuppressive action targeting the transmembrane protein CD20 expressed on pre-B and mature B cells. The CD20 protein biological function in B cells is not still fully understood, although it seems to be crucial for the BCR signaling and B-cell activation by acting as a calcium channel [2]. Moreover, CD20 is able to create complexes with other molecules such as CD53, CD81, and CD82 as well as to interact with major histocompatibility complex class II (MHCII) and CD40, which are involved in the interaction between B- and T-cells [2]. RTX seems to take action on T cell compartment too, by reducing T helper 1 (Th1) cells as well as increasing T helper 2 (Th2) and regulatory T (Treg) cells resulting with the imbalance between Th1 and Th2 cells, a typical phenotype of several immune dysregulatory disorders [2],[3].

Since its first approval by FDA in 1997 and by EMA in 1998 for relapsed or refractory, CD20-positive B-cell, low-grade or follicular non-Hodgkin's lymphoma (NHL), RTX has progressively received a wide range of both orphan and non-orphan indications, including other hematological malignances such as Chronic Lymphocytic Leukemia (CLL) and several autoimmune disorders. Indeed, RTX is used for the treatment of Rheumatoid Arthritis (RA), Immune Thrombocytopenic Purpura (ITP), Granulomatosis with Polyangiitis (GPA or Wegener Disease), Eosinophilic Granulomatosis with Polyangiitis (EGPA or Churg-Strauss syndrome), Microscopic Polyangiitis (MPA) and Pemphigus Vulgaris (PV) [4]. Over the last decades, the off-label use of RTX has widely increased, counting for more than 50% of cases. The main off-label uses are grouped into neurologic demyelinating diseases such as multiple sclerosis and autoimmune disorders such as Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis. RTX has also been widely administered off-label in other hematologic, oncologic, dermatologic and transplant settings [4], as well as in the context of primary antibody deficiencies (PADs) with autoimmunity and lymphoproliferation [3].

Immunologic effect and persistent post-RTX hypogammaglobulinemia

Since CD20 expression is limited to pre-B and mature B cells, hematopoietic stem cells and plasma cells are not affected by RTX immunosuppressive effect and, in most cases, allow for B cell immune reconstitution within 6 to 9 months after RTX administration [5]-[6]. Iatrogenic B cell impairment is mostly limited to naïve and unswitched IgM-committed B cell subsets and IgM decrease in RTX-treated patients. IgG/IgA-producing plasma cells lack CD20 expression [5], therefore, a drop of IgG/IgA is not a general trend but, when present, a faster restoring capacity is observed compared to IgM serum levels.[6] A significant impairment of humoral immune responses is not expected and recovery of normal B cells should occur within 12 months from the completion of treatment. However, as previously reported by us and other research groups, persistent hypogammaglobulinemia (PH) affecting all Ig isotypes can follow RTX administration in around 30-56% of patients, according to different reports [7]–[9]. The definition of PH remains arbitrary and it is mainly described as a post-RTX IgG deficiency, unlikely to recover after around 12 months.[10][11]. Nevertheless, specific vaccine antibody responses in addition to IgA and IgM isotypes might also be affected and abnormalities in memory B cell compartment, a predominance of naïve B cells [10][11], and a perturbation of the T cell compartment with prolonged CD4+ T cell lymphopenia have also been observed in the context of PH [12].

Assessing the “real-world” impact of B-cell targeting agents on humoral immunity and identification of a common pattern in PH is challenging for three main reasons: (i) lack of proper screening of patients before treatment and long-term follow-up to monitor delays in immune reconstitution [13]; (ii) definition of PH not universally accepted either because different groups adopted a wide range of thresholds of serum Ig levels as indication for immunoglobulin replacement therapy (IGRT) or because the sufficient monitoring to discern between transient and persistent hypogammaglobulinemia is unknown; (iii) the clinical significance of reduced IgG levels, as well as of other antibody isotypes, remains difficult to disclose, since the incidence of severe infections was variably reported and confounded by concomitant immune suppressive medications. Investigations in patients with impaired immune recovery suggest that halted differentiation from naïve to memory B cells, increased B-cell apoptosis and altered T lymphocyte homeostasis could be responsible for PH even in the context of normal circulating B cells [14]–[16]. This phenotypic

recurrent pattern has not found an unique association with a genetic predisposition, but both Fc-receptors polymorphism and undiagnosed common variable immunodeficiency (CVID) have been deemed to be responsible for these phenomena [17],[18].

Malignant disorders and transplant recipients

A phase I, dose-escalating trial investigating a chimeric monoclonal antibody targeting CD20 in 15 patients with non-Hodgkin lymphoma (NHL) first described no significant changes in immunoglobulin isotypes and partial recovery of B cells in a short-term follow-up (3 months) [19]. However, in a larger cohort of NHL patients (n=166) receiving a standardized dose of 375 mg/m^2 of RTX and four administrations, McLaughlin *et al.* reported a significant (>50% to subnormal levels) reduction of Ig levels in 14% of patients [20] and described normalization of B cells within 12 months after treatment. Following early pivotal reports establishing the efficacy of anti-CD20 mAb for B cell malignancies, several studies on both pediatric and adult patients with NHL confirmed that persistent IgG deficiency of at least one isotype can be observed in 15-50% of patients after RTX, depending on the different reports [21],[22]. Also, post-RTX PH has been observed in patients with HIV-associated lymphomas [23] and in patients after high dose chemotherapy [24],[25] as well as after stem cell transplant [14],[26]–[28]. Specifically, post-transplant Epstein Barr virus-associated lymphoproliferative disorder seems to be a high-risk condition for prolonged post-RTX hypogammaglobulinemia [29],[30]. Higher number of doses have been significantly associated with PH in patients with NHL [24],[31] by different groups, although data remain scarce and mainly retrospective. Similarly, the impact of concomitant treatment, such as steroids and purine analogues, has been variably reported as a relevant risk factor for post-RTX PH [24].Although post-RTX hypogammaglobulinemia in cancer patients or transplant recipients has been generally considered an iatrogenic effect of combining chemotherapy with anti-CD20 mAb in most patients, long-term depleting effect and lack of immune reconstitution limited to the B cell compartment remain poorly understood.

Autoimmune disorders

No association between post-RTX PH and specific background autoimmune disorders has been clearly documented, and irreversible hypogammaglobulinemia after anti-CD20 mAb therapy has been variably reported in several conditions where RTX use has now become common practice, including multiple sclerosis (MS) [32], nephrotic syndrome (NS) [33], systemic erythematous lupus [6], rheumatoid arthritis (RA) [34], vasculitis and autoimmune cytopenia [35]. In a retrospective study around 50% of adults (n=243) with vasculitis and other multi-systemic auto-immune disorders developed transient hypogammaglobulinemia during a median 42 months follow-up after receiving different RTX regimens (different doses, from single infusions to 6 monthly maintenance for 2 years), but only a small proportion of patients (4%) with severe IgG deficiency failed to restore normal Ig levels [36]. The same group, in a longer follow-up analysis on 142 patients, found persistent moderate and severe IgG hypogammaglobulinemia in 72% and 25%, respectively. More than one-third of patients required antibiotic prophylaxis to control recurrent infections and in 20% IGRT was started. Prior cyclophosphamide, ongoing prednisolone 12 months after RTX, nadir of IgG in the first 12 months of treatment and female sex were associated with moderate/severe hypogammaglobulinemia and/or IGRT use at 5 years, but no correlation was seen with the length of RTX exposure. An imbalance between naïve and memory B cells, with high naïve (IgM+IgD+CD27-) and low switched memory (IgM-IgD-CD27+) B cells, discerned patients with low Ig levels. A possible treatment effect and/or a sign of an underlying B cell dysfunction due to the association between autoimmunity and CVID condition was postulated [37]. Although the low numbers, as well as differences in background disorders and treatments, prevent any direct comparison between cohorts, it is worth noting that low Ig baseline levels has been commonly associated with a higher risk of PH [6],[36],[38],[39] while the role of different regimens and duration as well as of concomitant immunosuppressive treatments remain controversial in post-RTX PH in patients with autoimmune disorders [9],[40].

Post-RTX hypogammaglobulinemia in children and infectious risk

In-depth analysis on the prevalence of post-RTX hypogammaglobulinemia in children lagged behind the adult reports due to small cohorts, heterogeneity of baseline condition, lack of pre-treatment data or long-term follow-up. However, the incomplete maturation of B cell compartment in younger patients could potentially explain a higher frequency of impaired B cell recovery and PH than in adult reports. In a small retrospective single-center report on 9 patients with SLE who developed autoimmune thrombocytopenia and/or autoimmune hemolytic anemia, hypogammaglobulinemia

was found in 6 (67%), and only one patient, who showed low Ig levels and recurrent infections before RTX, required IGRT [41]. In another retrospective report on 63 children with different autoimmune disorders more than 40% developed post-RTX hypogammaglobulinemia, mainly in the first 6 months of therapy. Ig values were more severely and more persistently reduced in autoimmune CNS diseases *vs.* other conditions, with a higher rate of frequent and severe infections which required IGRT in more than 20% of cases [42]. In large cohort studies in children with highly heterogenous background, RTX-associated PH ranged from 13% to 30% [43],[44].

Importantly, most of these studies included a significant proportion of patients (up to 50%) that lacked baseline immunoglobulin levels or B cell counts before starting treatment with RTX. The absence of pre-treatment data represents a significant hurdle to establish the real incidence of post-RTX hypogammaglobulinemia and reflects the lack of awareness among clinicians using anti-B cell biologic drugs around the importance of a comprehensive baseline immunological assessment. Similarly, investigations of IgG levels > 12 months after RTX were available only for a proportion of patients. The lack of long-term follow-up also contributed to the ambiguity between transient drops of Ig isotypes and prolonged detection of low IgG levels requiring immunoglobulin replacement therapy.

Following small case series published in early 2010s [11],[35],[45], in 2019 we conducted a retrospective multicenter (16 centers from the Italian Network for Primary Immunodeficiency and Great Ormond Street Hospital London, UK) cohort study on 53 pediatric patients receiving RTX for autoimmune cytopenia with the aim to describe the kinetic of B cell recovery in a long-term follow-up, the incidence of Igs deficiency after RTX and a risk factor analysis for the occurrence of PH (> 12 months after RTX) [8]. We found a 32% incidence of PH (IgG < 2SD for age) after RTX, that was associated with delayed B cell recovery and low levels of IgA and IgM. It was noticeable that a significant higher percentage of patients with PH (29%) experienced infections requiring hospitalization, when compared to patients without PH (6%). A specific subgroup of patients that could be considered at higher risk for PH was also identified: the concomitance of other autoimmune conditions, younger age, response to RTX and a background of autoimmune haemolytic anemia or Evans Syndrome. This study represented the largest cohort of children with autoimmune cytopenia with post-RTX PH where pre-treatment status and long-term immunological follow-up were reported in details.

More recently in 2021 another large cohort of 207 children receiving RTX for an heterogenous background of autoimmune diseases and malignant conditions was described with a follow-up of more than 3 years [9]. Post-RTX incidence of low Ig levels significantly increased for all three Ig isotypes. Considering only patients with documented normal levels of Ig before treatment, IgM deficiency was the most common effect (55%), while 31% of patients showed reduced IgG. Using a similar definition of PH, 27% of patients was reported in the subgroup of patients where Ig were tested at least once 12 months after treatment. Those patients who experienced reduced Ig levels were also at higher risk of severe infections during follow-up.

These studies provided a comprehensive description of the kinetic of B cell recovery and Ig levels in subgroups of patients with comparable backgrounds. The long-term follow-up possibly contributed to the estimated prevalence of 25-35% of prolonged post-RTX hypo-IgG in children with benign conditions, higher than the one reported in most of adult cohorts. Nevertheless, the difficulties in establishing the pathogenetic role of RTX remain and the infectious risk related to hypogammaglobulinemia is heterogeneously addressed, with variables thresholds that trigger IGRT or limited only to symptomatic patients.

Risk of underlying PID

While hypogammaglobulinemia following biologic B cell targeting therapies might be regarded as an uncommon but expected iatrogenic effect, it is significantly more challenging to establish the pathogenetic role of B cell perturbation in patients that present a prolonged persistence of B cell aplasia and low Ig valuesn[8],[9],[11],[17],[23],[46]. The lack of proper pre-treatment assessment contributes to this confusion when hypogammaglobulinemia persists for years after treatment and selective B cell targeting might not be sufficient to explain the lack of immune recovery. Indeed, an impaired repopulation of the B cell compartment points towards an aberrant maturation of B cell progenitors (that are not tackled by RTX) into mature B cells, memory and plasma cells [14],[16],[47]. In this context, RTX might act as “stress” agent on an immune system with an inherent defect accelerating the emergence of a patent PID. This represents a change of perspective on how clinicians have looked at secondary/iatrogenic PH: initial case reports and recent series (**Table II**) suggest that patients with post-RTX PH could sporadically resemble the immune and clinical phenotype of common variable immunodeficiency (CVID). Two cohort studies investigating the long-

term follow-up of children with PH found that a significant proportion of these patients were eventually diagnosed as affected by a PID, rather than iatrogenic hypogammaglobulinemia[8],[9]. Specifically, we showed that in children affected by autoimmune cytopenia, RTX perturbation of peripheral blood B cells resulted in unveiling 9 cases of PID (17%): two patients eventually achieved a genetic diagnosis (ARTEMIS, PIK3cd), while in 7 cases a clinical diagnosis of CVID or other PADs was made. This group of patients was characterized by recurrent and severe infections, features of immune dysregulation and lymphoproliferation. When B cell sub-populations were investigated, switched-memory B cells proportion resulted absent or reduced (range 0-2%), even in patients with normal total B cells, suggesting an impairment of isotype class maturation [8]. Similarly, further 9 patients with PID diagnosis were identified in a cohort of children receiving RTX. Overall, incidence of PID in this cohort was 26% in the subgroup of children with refractory autoimmune cytopenia and most of them presented with Evans syndrome. Among these patients, a genetic diagnosis was achieved in 4/9 (NF-kB1, ADA2, TACI), while others presented features that allowed a clinical diagnosis of CVID (hypogammaglobulinemia, recurrent infections, lymphoproliferation, reduced switched memory B cells) [9].

Conclusions and practical considerations for RTX treatment

Recent evidence suggests that there are sub-groups of patients where the paradigm of secondary/iatrogenic hypogammaglobulinemia resulting from B cell depletion can not account for complex and atypical clinical manifestations arising after RTX treatment. Identification of previously undiagnosed inborn errors of immunity supports the need for an early recognition of those patients that might present a higher risk of PH and could benefit from a different approach. The lack of an immunology referral before administration of a biologic immunosuppressor is a critical limiting factor: in most studies baseline information on Ig levels and B cell counts is lacking and post-RTX immune defects are of difficult attribution if no comparison to pre-RTX status is possible. Therefore, a complete immune screening should always be advised before starting treatment (**Fig. 2**). Furthermore, some patients might require an in-depth investigation in the presence of specific red-flags. Most of the PIDs diagnosed after RTX firstly presented at a younger age with disorders typically associated with inborn errors of immunity (autoimmune cytopenia, EBV reactivation)[8],[9],[48]–

[50]. As the RTX indication might represent the first manifestation of an underlying immune impairment, a higher degree of suspicion in patients with atypical presentation and multiple autoimmune manifestation is warranted. Nevertheless, the profiling of patients at higher risk of PH and delayed recognition of PID is not complete and larger cohort of studies are needed. Equally important is the long-term follow-up of patients receiving RTX. Delayed B cell recovery more than 1 year after treatment is unlikely to resolve and might be associated with PH. However, it is worth noticing that several patients with PH showed normal total B cell population: only specific subset analysis of B cell compartment allowed to identify a switched memory deficiency that can account for the humoral immunity impairment [8],[9]. Still, the pathogenic mechanism of PH remains unclear in sporadic patients without an evident B cell defect, reflecting the limitations of available data. Therefore, a comprehensive immunological work-up is recommended in these patients: extensive B cell immunophenotype and Ig isotypes, but also free serum light chains and interrogation of candidate genes through NGS techniques.

Since its early clinical trials in patients with malignant disorder, RTX has found a growing field of applications in several autoimmune disorders in adults and children. Long-term follow-up allowed to identify patients that fail immune reconstitution and present with PH. These patients shouldn't always be regarded as affected by secondary immune deficiency as a proportion of children receiving RTX for immune dysregulation might harbor an inborn error of immunity, that has been unfolded by B cell perturbation. Therefore, clinicians should maintain a high level of suspicion and a prompt immunological referral is warranted.

Table I. B-cell targeting agents currently approved by FDA and EMA

Name of Agent	Type of Agent	Approved Indications
Rituximab [51]	anti-CD20 Chimeric IgG1 mAb	NHL, CLL, RA, ITP, GPA, MPA, EGPA, PV
Obinutuzumab [52]	anti-CD20 Humanized Glycoengineered IgG1 mAb	CLL, FL
Ocrelizumab [53]	anti-CD20 Humanized IgG1 mAb	MS
Daratumumab [54]	anti-CD38 Human IgG1 mAb	MM
Brentuximab Vedotin [55]	Anti-CD30 Chimeric IgG1 mAb conjugated with antimicrotubule agent monomethyl auristatin E (MMAE)	HL, Systemic anaplastic large cell lymphoma, Cutaneous T-cell lymphoma
Blinatumomab [56]	Bispecific T-cell engager molecule binding CD19 expressed on B-lineage origin surface and CD3 expressed on the T-cells surface	CD19-positive relapsed or refractory B-precursor ALL, Philadelphia chromosome negative CD19-positive B-precursor ALL
Inotuzumab ozogamicin [57]	Anti-CD22 Recombinant Humanized IgG4 kappa mAb covalently linked to N-acetyl-gamma-calicheamicin dimethylhydrazide.	Relapsed or refractory CD22-positive B cell precursor ALL. Patients with Philadelphia chromosome-positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 TKI.
Belimumab [58]	Anti-soluble BAFF (BLyS) Human IgG1 lambda mAb	Active autoantibody-positive SLE with a high degree of disease activity despite standard therapy; active

		lupus nephritis
Bortezomib [59]	26S proteasome inhibitor	MM, mantle cell lymphoma
Carfilzomib [60]	20S proteasome inhibitor	MM
Eculizumab [61]	Recombinant humanized monoclonal IgG2/4k antibody binding the human C5 complement protein	PNH, aHUS; Refractory gMG in AChR antibody-positive patients; NMOSD in AQP4 antibody-positive patients
Ravulizumab [62]	Monoclonal IgG2/4k antibody binding the human C5 complement protein	PNH; aHUS;

Abbreviations: AChR: ACetylcholine Receptor ALL: Acute Lymphoblastic Leukemia; AQP4: Anti-aQuaPorin-4; aHUS: Atypical Haemolytic Uremic Syndrome; CLL: Chronic Lymphocytic Leukemia; EGPA: Eosinophilic Granulomatosis with Polyangiitis; FL: Follicular Lymphoma; generalized Myasthenia Gravis (gMG); GPA: Granulomatosis with Polyangiitis; HL: Hodgkin Lymphoma; ITP: Immune Thrombocytopenic Purpura; MM: Multiple Myeloma; MPA: Microscopic Polyangiitis; MS: Multiple Sclerosis; NHL: Non-Hodgkin Lymphoma; Neuromyelitis Optica Spectrum Disorder (NMOSD); PNH: Paroxysmal nocturnal haemoglobinuria; PV: Pemphigus Vulgaris; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; TKI: Tyrosine Kinase Inhibitor.

Table 2. PID diagnosis in children with post-RTX persistent hypogammaglobulinemia.

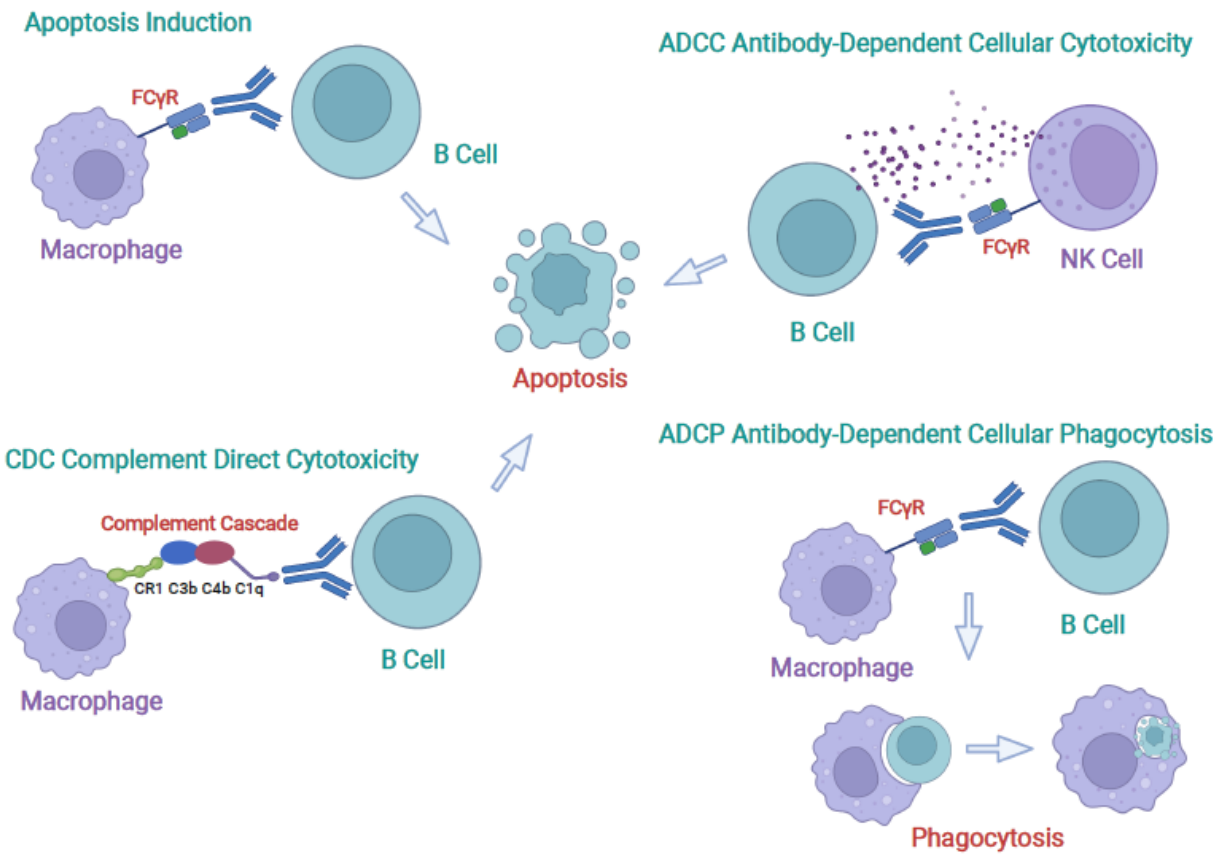
RTX indication	Age	Reduced B cells	Reduced Memory B cells	Final diagnosis	Reference
ITP	nd	nd	nd	CVID	Bussel [50]
ES	19	Y	Y	*PIK3cd*	Kaplan [11]
Autoimmune sinusitis, lung disease and GI disease	nd	nd	nd	*RAG1*	Bonagura [48]
ITP	24	Y	nd	*FASL*	Viallard [49]
ITP	14	N	Y	CVID	Levy [35]
ITP	45	N	Y	CVID	
AHA	2	Y	nd	*ARTEMIS*	Ottaviano [8]
AHA	1.3	N	Y	*PIK3cd*	
ITP	10	N	Y	CVID	
ITP	7	Y	Y	CVID	
AHA	1.2	Y	Y	PAD	
AHA	10	N	nd	PAD	
ITP	11.6	N	Y	CVID	
AHA	14	N	Y	CVID	

AHA	4.7	N	Y	CVID	
ES	9	N	Y	*NFKB1*	Labrosse [9]
ES	7	N	N	*NFKB1*	
ES	5	Y	Y	CVID	
EBV control	1.8	Y	Y	HLH	
ES	3	Y	Y	CVID	
EBV control	2	N	Y	HLH	
ES	4	N	N	*TACI*	
ITP	3	N	N	Selective IgM def	
ES	1.1	N	N	*ADA2*	

Abbreviations:

Y: Yes; N: No; ND: No Data

AHA: Autoimmune hemolytic anemia; CVID: Common Variable Immunodeficiency; EBV: Epstein-Barr Virus; ES: Evans Syndrome; FasL: Fas Ligand; HLH: Hemophagocytic Lymphohistiocytosis; ITP: Immune Thrombocytopenic Purpura; NFKB1: Nuclear Factor Kappa B Subunit 1; PAD: Primary Antibody Deficiency; PIK3cd: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta; RAG1: Recombination Activating 1; TACI: Transmembrane activator and CAML interactor.



FIGURES

Fig. 1 Principal mechanisms of action of B cell-targeting biologicals leading to B cell depletion

Iatrogenic B cell depletion could be induced by A) Transmembrane signalling and apoptosis through Fcγ receptor expressed on human macrophages; B) ADCC Antibody-Dependent Cellular Cytotoxicity: NK cells are activated through their Fcγ receptor which leads to B-cell lysis by perforin and granzymes liberation; C) CDC Complement Direct Cytotoxicity: the C1 complement complex is recruited through antibody's Fc domain, leading to proteolytic cascade activation. The consequent production of membrane attack complex (MAC) into B cells membranes causes lytic pores and cell death; D) ADCP Antibody-Dependent Cellular Phagocytosis: macrophages are activated through their Fcγ receptor which leads to B cell engulfment and intracellular phagosome formation.

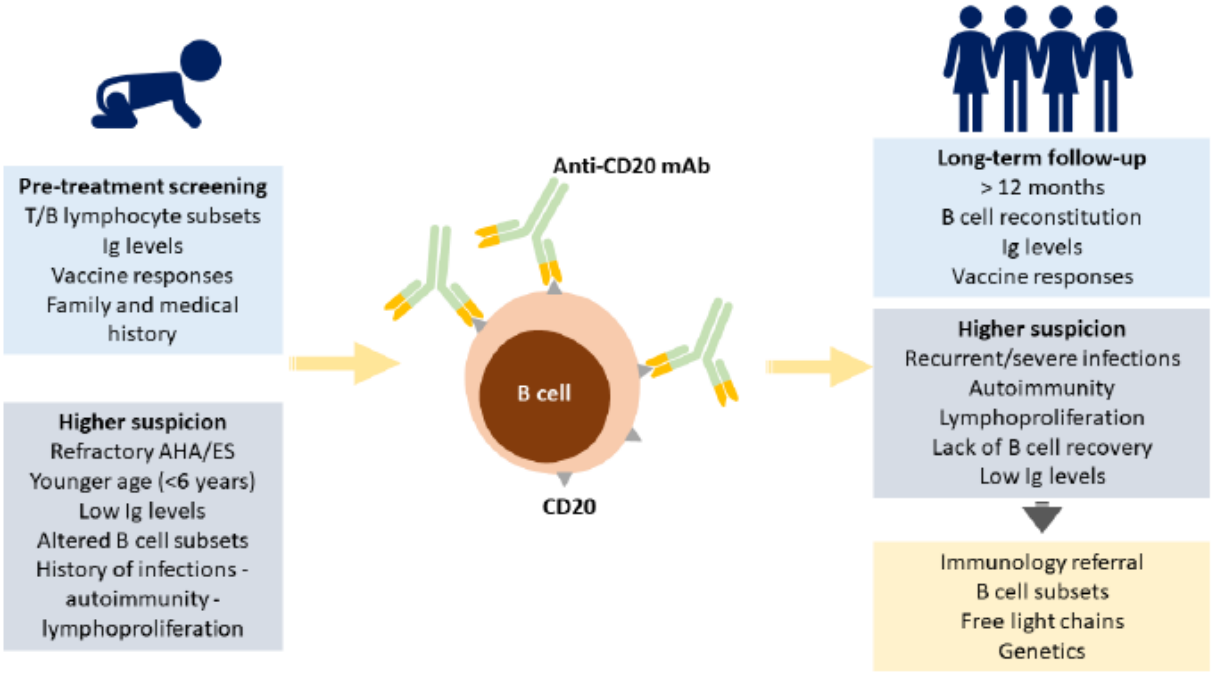


Fig. 2 Proposed outline to address hurdles in differential diagnosis between primary and secondary hypogammaglobulinemia in patients receiving anti-CD20 mAb. Basic immunological investigation before starting treatment should include lymphocyte subsets, serum Ig levels, vaccine responses. A higher degree of suspicion for potential underlying PID is warranted in patients with specific background or baseline immunological abnormalities. Equally important, long-term follow-up should be offered to all patients to monitor normal B cell recovery and onset of hypogammaglobulinemia. Specific red-flags such as impaired immune reconstitution, new-onset autoimmunity or infections should trigger in-depth immunological investigations.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflict of interest

The author declares no commercial or financial conflict of interest.

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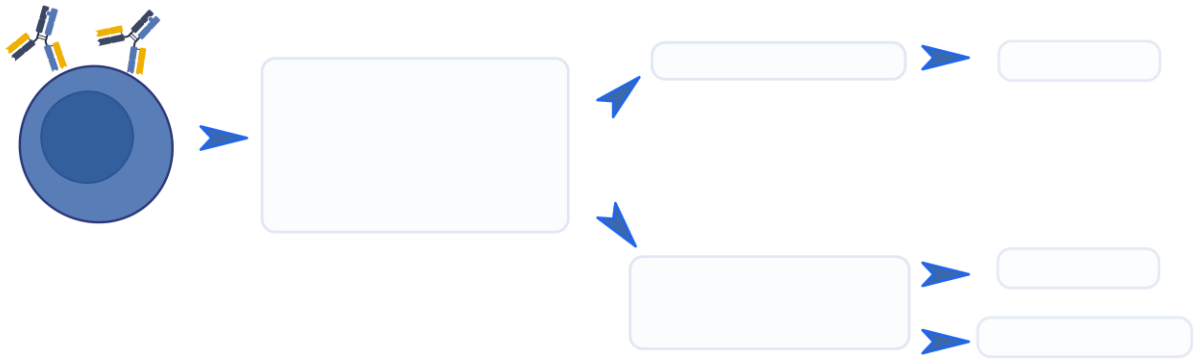

Rituximab and other B-cell targeting biologicals carry out their immunosuppressive effect by inducing B cell depletion, but hypogammaglobulinemia, vaccine specific antibody defect or T cells impairment can also occur. B cell immune reconstitution is generally expected within 12 months after treatment, framing a condition of transient secondary immunodeficiency (SID). However, in some cases, persistent hypogammaglobulinemia (>12 months) might occur, which could underlie a previously undiagnosed inborn error of immunity unveiled by iatrogenic B-cell perturbation.